The Obsessive-Compulsive and Tic-related Brain

de Vries, F.E.

2016

document version
Publisher's PDF, also known as Version of record

Chapter 1

General introduction

An introduction to obsessive-compulsive disorder and Tourette's Syndrome

The introduction to this thesis (**Part I**) will first provide a short overview of clinical characteristics of Tourette's Syndrome and obsessive-compulsive disorder, followed by a review of putative neurobiological mechanisms involved in both disorders and the methods that may be used to gain further insight into these mechanisms. This chapter concludes with stating the aims of the thesis and providing an overview of the studies that are described in the following chapters.

Obsessive-compulsive disorder (OCD) and Tourette's Syndrome (TS) are both neuropsychiatric disorders often with a childhood onset (Bloch and Leckman, 2009;Rapoport et al., 1992). OCD is characterized by obsessions defined as repetitive and intrusive, ego-dystonic thoughts that cause anxiety and/ or tension (American Psychiatric Association, 2013). Examples of obsessions are fear of contamination, fear of unintentionally harming others, a need for symmetry/ "just-not-right- perceptions" and religious, aggressive or sexual taboo thoughts. Compulsions are the repetitive and ritualized behaviors performed to reduce anxiety or distress, caused by the obsessions, in the short term. Paradoxically this results in sustaining anxiety over the long term. Examples of compulsions are excessive washing and cleaning related to contamination fear, continuous checking to avoid harm, ordering objects until they are 'just right', and rituals such as counting, touching certain objects or thinking neutralizing thoughts (Cath et al., 2011). These obsessions and compulsions take up at least one hour a day or cause significant impairment in daily life (American Psychiatric Association, 2013). The lifetime prevalence rate of OCD in the community is estimated between 0.9% in the Netherlands (de Bruijn et al., 2010) and 2.3% in the US (Ruscio et al., 2010), however subthreshold symptoms are much more common with an estimated prevalence between 4.9% and 28% (Ruscio et al., 2010;de Bruijn et al., 2010). OCD has a bimodal pattern of age-at-onset with an early peak around 13 years and a second peak around 25 years (Anholt et al., 2014). Despite available treatment strategies such as cognitive behavioral therapy and pharmacotherapy, OCD often runs a chronic long-term course. Of the 83 patients included in various treatment studies, only 20% showed remission at 10-20 years follow-up (Bloch et al., 2013), which is in line with the 40-year follow-up study by Skoog en Skoog (1999), reporting that 20% of the patients completely remitted and that 28% recovered with persistent subclinical symptoms.

The presence of tics is the hallmark feature of TS. Tics are involuntary, sudden movements (motor tics) or sounds (phonic tics) that occur many times a day in bouts, but can also be temporarily suppressed. TS requires the presence of both motor and phonic tics (although not necessarily at the same time) that are present for at least a year and start before the age of 18, but in most cases tics appear before the age of ten years. If only motor or phonic tics are present, chronic tic disorder is diagnosed instead of TS (American Psychiatric Association, 2013). Tics may be either simple movements or sounds (such as eye blinking or throat clearing) or complex, involving a combination

of movements or the uttering of words or sentences. Prevalence of TS and chronic tic disorder is estimated around 0.8% for TS, 1% for chronic tic disorder and around 3% for transient tic disorder (Scharf et al., 2012;Knight et al., 2012). In contrast to OCD, in about 75% of the patients tic severity greatly declines in early adulthood and about a third reaches complete remission (Bloch et al., 2009;Bloch and Leckman, 2009).

There is considerable overlap between OCD and tic disorders (characteristics of both disorders are summarized in Table 1.1). First, the disorders often co-occur. Tic-disorders are reported in 17-29% of adult OCD patients (Eisen et al., 2010;Gomes de Alvarenga et al., 2012;Nestadt et al., 2009) and between 20-50% of TS patients are also diagnosed with OCD (Hirschtritt et al., 2015;Scharf et al., 2012). Moreover, genetic family studies have shown increased rates of OCD in relatives of TS patients (Pauls et al., 1986;Pauls et al., 1991), as well as higher rates of tics in family members of OCD patients (Pauls et al., 1986;Pauls et al., 1991;Hanna et al., 2005;do Rosario-Campos et al., 2005), suggesting a shared genetic background. This was recently corroborated in a large population based study, showing increased cross-disorder recurrence rates in family members of index patients affected with OCD or TS (Browne et al., 2015). A genetic correlation between TS and OCD was estimated at 0.41 using genome wide complex trait analysis (Davis et al., 2013), although this relationship is complex, as a polygenic score calculation from a Genome Wide Association Study (GWAS) study in the combined GWAS sample of OCD and TS did not show overlap in polygenic scores for both disorders (Yu et al., 2015). Second, tics and compulsions show phenomenological similarities; they are both considered repetitive behaviors that are partially under voluntary control. Typically, a compulsion is performed to reduce anxiety or distress caused by an obsession and can thus be considered as intentional or goal-directed behavior. Analogously, a tic may be preceded by a feeling of discomfort or tension (also called a premonitory urge) that is relieved after performing the tic (Scahill et al., 1995;Leckman et al., 1993). Complex, ritual-like tics may be difficult to differentiate from compulsions (Worbe et al., 2010b). The overlap between TS and OCD is most pronounced in childhood-onset OCD that more often affects boys, in which increased prevalence rates of tics occur and which is more often characterized by symmetry/ordering symptoms (including counting and touching rituals), symptoms that are also more frequently present in TS (Cath et al., 2001a;Cath et al., 2001b;Rosario-Campos et al., 2001;do Rosario-Campos et al., 2005).Third, both disorders are thought to result from partially similar neurobiological disturbances in fronto-striatal circuits, which will be covered in the next paragraph.

Table 1.1 Summary of characteristics of OCD and TS

	Obsessive-compulsive disorder	Tourette's Syndrome
Mean age at onset	A peak around 13 years and a peak around 25 years	Around 7 years (mostly before 10 years)
Prevalence	Around 2%	Around 1%
Male: female ratio	More or less equal	3:1
Heritability	37-47%	58-77%
Course	Often chronic, waxing and waning or episodic course. If untreated usually persistent.	About 75% decline in early adulthood and 30% is tic-free
Repetitive behaviors		
Perceived as	Ego dystonic	Ego syntonic
Precipitating phenomenon	Obsessional thoughts provoke anxiety that is reduced after performing compulsions.	Premonitory urge, tension is relieved after performing tics
Control over repetitive behavior	Suppression is possible but anxiety often increases.	Suppression is possible but tension often increases.
Treatment		
psychotherapy	Exposure-in vivo with response prevention	Exposure-in vivo with response prevention or habit reversal
pharmacotherapy	Serotonergic antidepressant(SSRI or clomipramine) DA receptor antagonists in addition to SSRI	DA receptor antagonists, DA modulators or clonidine. SSRIs when comorbid OCD is present

Neurobiology of obsessive-compulsive disorder and Tourette's Syndrome

The high rates of comorbidity between TS and OCD, the similarities in phenotypic expression and some overlap in genetic background motivate an investigation into possible common neurobiological mechanisms associated with both disorders.

A role for the fronto-striatal circuits in the neurobiology of TS and OCD was first suggested by clinical observations. Acquired lesions, such as trauma, neurodegeneration or immunological processes as a result of infections at the level of the basal ganglia and prefrontal cortex can result in onset of OCD and tics (Figee et al., 2013;Swedo et al., 1989;Swedo et al., 1989;Robertson, 2000;Landau et al., 2012). The basal ganglia include the striatum (caudate nucleus, putamen and nucleus accumbens), the globus pallidus with an internal and external segment (GPi and GPe), the subthalamic nucleus (STN) and the substantia nigra (SN) and are connected to cortical areas by multiple

interconnected recurrent loops that project from the cortex to the striatum, through the thalamus and back to the cortex (see Figure 1.1). These so-called cortico-striatal-thalamico-cortico (CSTC) loops function partially in a segregated way to serve different functions; motor loops project from the motor cortex to dorsal parts of the putamen and are involved in motor control and habit learning, whereas associative circuits that connect the caudate and the dorsolateral prefrontal cortex (dlPFC) are thought to play a role in goal-directed behavior, and limbic loops involved in reward learning and motivational behavior are represented in the ventral parts of the striatum and project to the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) (Alexander et al., 1986;Haber, 2003;Jahanshahi et al., 2015).

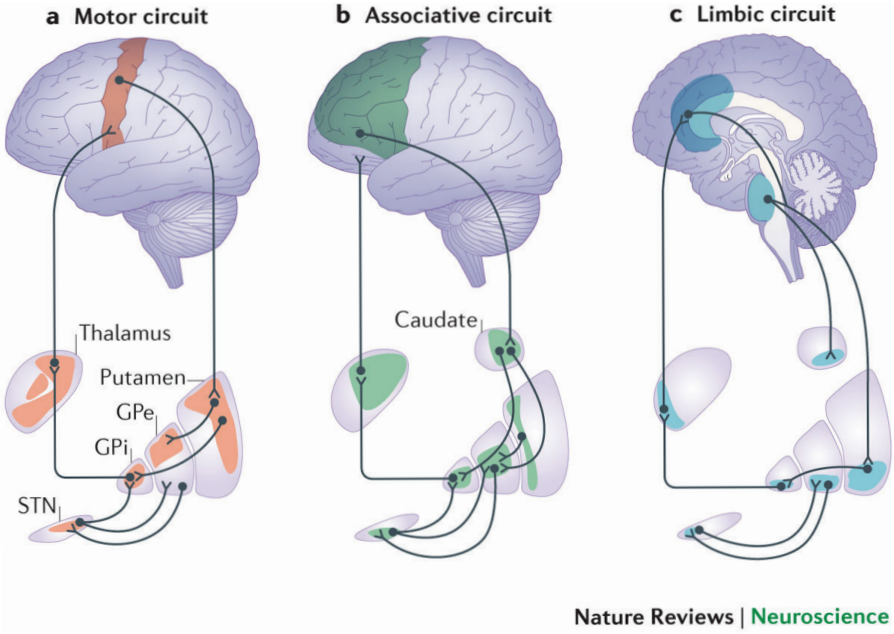
The basal ganglia operate through mechanisms of inhibition, facilitation and disinhibition, mediated by several neurotransmitters and result in the selection of context-appropriate actions and inhibition of other actions. Excitatory (glutamatergic) projections run from the cortex to the striatum and in the striatum these are modulated by two opposing dopaminergic pathways. In the direct pathway dopamine acts (predominantly) on D_1 receptors and increases striatal excitation, followed by inhibition of the GPi, which leads to disinhibition of the thalamus and excitation of the specific cortical areas that belong to the involved CSTC circuit. Thus, the direct pathway has a net excitatory effect. The D_2 receptor mediated indirect pathway leads to excitation of the GPe, (GABA-ergic) inhibition of the STN and excitation of the GPi, resulting in inhibition of the thalamus and decreased excitation of the cortex. An increase in dopamine induces an imbalance favoring activity in the direct pathway over the indirect pathway and biases the gating of the basal ganglia towards behavioral activation and reinforcement. Considering only the two dopaminergic pathways, however, is an oversimplification of the basal ganglia circuitry, as disruption of other inhibitory mechanisms within the basal ganglia, such as dysfunction of the "fast-spiking" GABA-ergic interneurons, or an increase in glutamatergic activity in the hyperdirect pathway (an excitatory cortico-subthalamico-pallidal pathway), could also result in disinhibited behavior (Tremblay et al., 2015).

CSTC dysfunction has been proposed as a pathophysiological mechanism underlying both OCD and TS (Mink, 2001;Menzies et al., 2008a), although in each disorder different loops may be involved. For instance, TS was associated with an imbalance in the sensorimotor-putamen circuits (Mink, 2001;Sowell et al., 2008;Neuner et al., 2014) and OCD could result from changes in the emotional OFC/ACC-caudate loops (Remijnse et al., 2005;Chamberlain et al., 2008). Current opinions, however, state that this is an oversimplification and the complex behavioral pattern in both disorders is more likely to arise through an *interplay* between disturbed sensorimotor, associative, and limbic circuits (Worbe et al., 2015;van den Heuvel et al., 2015). For TS clinical heterogeneity is associated with structural changes in different CSTC loops, e.g. changes in motor cortex were related to simple motor tics, changes in associative loops with

complex tics and disturbances in emotional loops were associated with OC behavior (Worbe et al., 2010a). Moreover, for OCD several models have been put forward that include brain alterations beyond (orbito)fronto-striatal pathways, coupling (functional) neuro-anatomical changes to neuropsychological dysfunction. For example, Milad and Rauch (2012) suggested studies should investigate fear conditioning and deficits in fear extinction learning in OCD compatible with a role for medial OFC, dorsal ACC, but also in the amygdala and hippocampus (a fronto-striato-limbic model). Another theory posits that orbitofronto-striatal hyperactivity in OCD disrupts goal-directed behavior, favoring activity in the putamen and excessive habit formation (analogous to addictive behavior) as the underlying mechanism of compulsions. Moreover, obsessions may be a post-hoc rationalization for these behaviors, instead of the trigger of compulsive behavior (Gillan and Robbins, 2014;Gillan et al., 2011).

Based on Phillips et al. (2003) a model for OCD was proposed, based on a relative imbalance between ventral and dorsal cortico-striatal circuits (equivalent to the emotional and associative CSTC loops respectively). It was hypothesized that OC symptoms may result from a stronger influence of the D_1 mediated direct pathway in ventral-striatal circuits and a stronger inhibitory D_2 influence on the indirect pathway in the dorsal cognitive control circuits (Remijnse et al., 2005;Mataix-Cols and van den Heuvel, 2006). An extended version of this model included anxiety and OC spectrum disorders, resulting in a spectrum in which anxiety disorders arise preliminary from dysfunction of limbic brain structures and TS from (sensorimotor) fronto-striatal disturbances. Obsessive-compulsive behavior is positioned in the middle of the spectrum with contributions from both limbic and fronto-striatal circuits. It has been speculated that within the category of OCD, patients with symmetry/ordering symptoms are closer to TS and have more fronto-striatal involvement whereas OCD patients with prominent contamination fear may be closer to the anxiety disorders and the limbic end of the spectrum (Mataix-Cols and van den Heuvel, 2006). According to the model of ventral-dorsal imbalance, OCD may arise from reduced (dorsal) executive control over obsessions and compulsive behavior, implying dysfunction of the fronto-parietal and/or cingulo-opercular cognitive control networks (Dosenbach et al., 2008) and executive dysfunction in OCD. Indeed, large neuroimaging studies indicated structural changes in OCD patients in the cingulo-opercular network; the anterior insula, ACC and dorsomedial PFC (Radua et al., 2010;de Wit et al., 2014). Furthermore, executive dysfunction such as deficits in planning and response inhibition has consistently been found in OCD (Kuelz et al., 2004;Chamberlain et al., 2005;Greisberg and McKay, 2003) as well as dysfunction of the fronto-parietal network (van den Heuvel et al., 2005;Menzies et al., 2008b).

Alternatively, OCD and TS may be conceptualized as disorders on the impulsive-compulsive spectrum. Impulsivity is defined as rapid and unplanned reactions to internal or external stimuli and compulsivity as repetitive and habitual acts that are



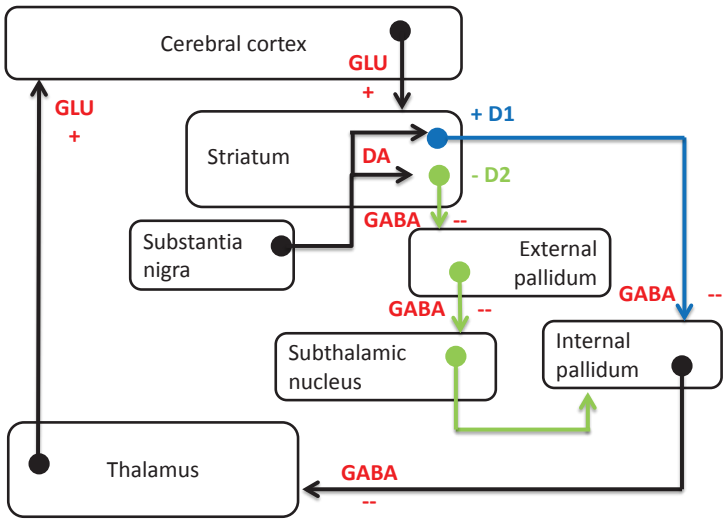


Figure 1.1

Upper panel: Basal ganglia and the different functional cortico-striato-thalamo-cortical (CSTC) circuits. Reprinted with permission from Macmillan Publishers Ltd: Nature Neuroscience (Jahanshahi et al., 2015). Lower panel: Schematic representation of the CSTC circuits GPe= globus pallidus externa GPi= globus pallidus interna STN= subthalamic nucleus

Glu= excitatory glutamate projections, GABA= inhibitory GABA projections. DA= dopamine. Blue line= the D_1 receptor mediated direct pathway with a net excitatory effect. Green line= the D_2 receptor mediated indirect pathway with a net inhibitory effect.

performed to prevent a perceived negative consequence. Both phenomena are thought to be involved in behavioral disinhibition but have separate putative neural pathways; compulsivity involves activity in the orbitofronto-striatal circuits and impulsivity activity in the circuits between subgenual ACC and ventral striatum. Compulsivity and impulsivity are mediated by several neurotransmitters (dopamine, serotonine, noradrenaline), but the response may be non-linear and depend on receptor subtypes (van Velzen et al., 2014;Fineberg et al., 2010). Clinical observations support hypotheses about a hyperdopaminergic state in TS and OCD; D_2 receptor antagonists are effective in the treatment of TS and as an augmentation strategy to SSRIs in OCD (Bloch et al., 2006;Vulink et al., 2009) and conversely dopamine agonists may provoke tics and induce compulsive behaviors (Borcherding et al., 1990). Several molecular imaging studies have supported this model for TS although some results are conflicting (reviewed in (Gerard and Peterson, 2003)). So far, the few reports on dopamine receptor binding in OCD have also shown evidence for increased dopaminergic neurotransmission (Denys et al., 2004;Olver et al., 2009;Perani et al., 2008). Two previous studies have reported an increased striatal dopamine release in TS patients compared to controls (Singer et al., 2002;Wong et al., 2008). In the larger of these two studies, the majority of the patients had a comorbid diagnosis of OCD (10 out of 14 included patients;(Wong et al., 2008)) and it remains uncertain if TS patients without OCD and OCD patients without tics are also characterized by increased dopamine release.

Searching for endophenotypes, an OCD family study

Altered brain activity in patients (as described above) could indicate either a pathological *state* (e.g. the activity is a consequence of having symptoms or related to efforts to suppress symptoms), or could be related to a genetic vulnerability (*trait*) underlying the disease. A promising approach to gain more insight in this aspect of the neurobiology of OCD is to search for intermediate markers of brain dysfunction (endophenotypes) that are closer to genetic factors and underlying pathology than the heterogeneous symptoms and may thus guide the search for contributing genes (Chamberlain and Menzies, 2009). An endophenotype reflects the genetic vulnerability for a disease (trait mark), is relatively independent from disease severity (e.g. is also present in remitted patients) and is more often present in unaffected relatives than in the general population (Gottesman and Gould, 2003). Therefore a design in which patients are compared to unaffected relatives (with increased genetic risk to develop the disease) and an unrelated comparison group could help to identify putative endophenotypes. Previous family studies of OCD have suggested deficits in response inhibition, cognitive inflexibility and planning as possible endophenotypes (Chamberlain et al., 2007;Chamberlain et al., 2008;Menzies et al., 2007;Delorme et al., 2007). As was mentioned in a previous paragraph, dysfunction of (cingulo-opercular and fronto-parietal) cognitive control networks is one possible mechanism underlying OCD. Investigating these networks in

OCD and their unaffected relatives could thus contribute to understanding vulnerability markers and protective mechanisms.

Aims and outlines of the thesis

TS and OCD show considerable overlap in phenotype, neurobiology and treatment, and frequently co-occur. Neuro-anatomical models for TS and OCD indicate a role for the basal ganglia and connected thalamo-cortical circuits and for fronto-parietal and cingulo-opercular (cognitive control) networks and limbic areas. Moreover, hyperactivity in the CSTC circuits may be driven by increased dopaminergic neurotransmission, disrupting the balance between the direct and indirect pathways that leads to behavioral disinhibition. For OCD it has been hypothesized that this imbalance may differentially affect ventral and dorsal CSTC circuits, favoring emotional processes over cognitive control. Despite these commonalities, OCD and TS are categorized in different chapters in the DSM-5, with OCD in the new chapter of the OC spectrum disorders and TS in the chapter of neurodevelopmental disorders. We believe that it is important to study OCD and TS in concert to identify common and distinct phenomenological and neurobiological aspects. Furthermore, to increase the understanding of whether underlying neurobiological deficits reflect state or trait vulnerabilities, an endophenotype approach is of high interest.

In **Part II** (**Chapters 2, 3 and 4**) of this thesis the crossroads between both disorders are studied by investigating tic-related OCD, OC behavior in TS and by making a direct comparison between OCD without comorbid tics and TS without comorbid OCD. In **Chapter 2** we aimed to better define and understand the clinical characteristics and course of the tic-related subtype of OCD, since previous reports have been inconclusive. We used data from the Netherlands OCD Association (NOCDA) study. This is an ongoing naturalistic cohort study, aiming to establish the course of OCD and the determinants of long-term outcome. Data collection started in 2005 and a total of 419 patients with OCD were included. Systematic comprehensive measurements on OCD symptoms, psychiatric comorbidity, physical health, quality of life, use of medication (and more) were performed at baseline and follow-up measurements took place after two-years. The third wave of data has been collected as well and an additional wave is planned at six year follow-up (Schuurmans et al., 2012). Within this cohort we studied 270 patients with tic-free OCD and 107 patients with tic-related OCD and compared them in a cross-sectional approach to study differences in clinical characteristics. We then applied linear mixed model analysis to study longitudinal follow-up to investigate the natural course of OC severity in both groups.

Symmetry behavior is common in TS and has been qualified either as complex tics or as OC behavior. We aimed to increase the understanding of symmetry behavior in TS and to further characterize it within the limbic to fronto-striatal spectrum suggested by

other studies (Mataix-Cols and van den Heuvel, 2006). If symmetry behavior is similar to complex tics, predominant involvement of motor circuits would be expected and if it shows more similarities with OC behavior limbic circuits may be involved. In **Chapter 3** we studied the neural correlates of symmetry and ordering behavior in 14 patients with TS and 10 matched comparison subjects. For this study $H_2{}^{15}O$-Positron Emission Tomography (PET) imaging was used (see Box 1 with applied imaging techniques), during which subjects were shown pictures of either organized and symmetrical or disorganized and asymmetrical objects/scenes to induce symmetry behavior.

Hyperdopaminergic neurotransmission may result in an imbalance between the direct and indirect cortico-striatal pathways and is hypothesized to play a role in TS and in OCD. Previous studies indicated an increased phasic dopamine response in TS patients with comorbid OCD. We aimed to investigate if the role of dopaminergic neurotransmission is similar in TS without OCD and in OCD without tics. In **Chapter 4**, we compared tonic and phasic dopamine neurotransmission between 12 OCD patients without tics, 12 TS patients without OCD and 12 comparison subjects using [^{11}C]-raclopride PET imaging (see Box 1 for further explanation of the used paradigm).

Part III of the thesis (**Chapters 5, 6 and 7**) focuses on the neural correlates of executive function in OCD patients using a family study design, as it permits differentiating between genetic vulnerability for OCD (trait aspects) or potential deficits as a consequence of having OCD (state aspects). We aimed to identify putative neurocognitive endophenotypes for OCD to better understand the underlying pathology of the disorder and to aid a future search for genetic contributions to OCD.

For the family study task-based and resting state functional MRI scans were acquired (see Box 1) in 43 un-medicated OCD patients and 19 of their unaffected siblings to compare them to a group of 38 matched comparison subjects (without OCD or a family history of OCD). Only a part of all the data that were collected during this study is presented in this thesis and some data are still in preparation or published in different theses. Box 2 gives an overview of the full study protocol and the data that were acquired data. One aim of establishing endophenotypes is that it can aid the search for specific genetic pathways involved in OCD. And although samples for genotyping were collected in the participants, investigating these genetic pathways was outside of the scope of this thesis.

Executive function relies on fronto-parietal and cingulo-opercular networks and a deficit in executive function is a candidate endophenotype of OCD. In **Chapter 5** we aimed to investigate deficits in response inhibition by using the stop-signal task. The three groups were compared with regard to task performance and brain activity during successful response inhibition. In **Chapter 6** we studied working memory and used an n-back task to probe the fronto-parietal circuits. Both task performance and brain activity during the task were compared between the three groups. Connectivity

between the task-related executive network and the amygdala was also investigated for each group. Following up on the two studies of executive function using a task-based paradigm, in **Chapter 7** we aimed to study alterations in functional connectivity at rest within and between cognitive control and limbic networks in OCD. A second aim was to test if altered functional connectivity could qualify as a possible endophenotype. For this aim, resting state fMRI was used to compare OCD patients with unaffected relatives and controls.

Finally **part IV** of the thesis contains a summary of the previous chapters and a general discussion with methodological considerations, implications, and suggestions for future research (**Chapter 8**) as well as a summary of the thesis in Dutch (**Chapter 9**).

Box 1: applied imaging techniques

Functional Magnetic Resonance Imaging (fMRI) is based on the assumption that an increase in local use of oxygenated blood, supplied by the vasculature, indicates increased neuronal activity in that area. As deoxygenated hemoglobin has paramagnetic properties, a change in oxygenation can be detected by the MR scanner and is reflected in a change in the blood-oxygenated level dependent (BOLD) contrast. The BOLD signal is thus an indirect measurement of neuronal metabolic activity.

During **resting state fMRI** participants lie still in the scanner, usually with their eyes closed and can let their minds wander naturally. The spontaneous fluctuations in the BOLD signal are measured over a period of time, resulting in a timecourse for each voxel in the scanned brain. These low frequency fluctuations show high correlations (or synchronization) between distant brain areas that are considered functional networks, since the same areas are co-active during the performance of specific tasks. It is thought that the coherence of resting-state networks is related to its function during task-performance. The resting state approach has the advantage that it may be applied to subjects that are not able to perform difficult tasks (such as children or cognitively impaired individuals). A disadvantage of this technique is that it is susceptible to artifacts and noise (such as movement and cardio-respiratory effects) that need to be controlled for rigorously.

Task-related fMRI is used to study areas in the brain necessary to support the execution of simple or more complex tasks. For example: A simple finger tapping task will primarily activate contralateral motor cortex, but also other areas in the motor network (ipsilateral motor cortex, premotor areas, cerebellum) are activated. During task-related fMRI, participants perform a task in the scanner

alternated with epochs during which participants may passively view a screen or perform a control task, usually with low cognitive demands. When analyzing functional imaging data, (the timecourse of) task and control conditions are contrasted to identify the brain areas that show increased activity during the task.

Task-related functional connectivity combines the above mentioned techniques. It measures the change (task versus baseline condition) in connectivity between the timecourse in a defined seed region and other areas in the brain.

Positron Emission Tomography (PET) is an imaging technique that detects intravenously injected radioactively labeled compounds and produces a quantitative three-dimensional image of the compound in the body.

$H_2{}^{15}O$-PET neuroimaging, as in fMRI, is based on the assumption that increased regional cerebral blood flow (rCBF) reflects increased neuronal activity. The quantity of rCBF is measured through injecting radioactively labeled water in subjects that can be measured by the PET camera. Similar to fMRI, active conditions are contrasted with control conditions to test what brain areas show increased activity during a task condition. When comparing fMRI with PET, fMRI has a higher spatial and temporal resolution, is less invasive and cheaper than PET. PET imaging is more suitable for subjects with claustrophobia that cannot tolerate being in an MR scanner, has less signal dropout in limbic regions such as the OFC and the amygdala and is less susceptible to scanner drift, making it more suitable to measure slow processes (e.g. comparing the beginning vs. the end of a scan session).

In **ligand PET** an intravenously injected radio-labeled ligand binds to a specific receptor or other compound in the brain. Tracers are available for the GABA receptor, serotonergic and dopaminergic transporters, pre- and post-synaptic dopamine receptors to name a few. **[^{11}C]-raclopride** is a low affinity $D_{2/3}$ receptor antagonist and it competes with dopamine for binding to the postsynaptic receptors. Therefore, it is an indirect measure of synaptic dopamine availability, as higher binding suggests less competition with dopamine. At rest, neurons release dopamine in a tonic fashion, keeping the dopamine concentration constant, but upon activation a phasic response is generated, characterized by the release of high concentrations of dopamine into the synapse. Intravenous administration of amphetamine results in dopamine release, mimicking this phasic response. When [^{11}C]-raclopride scans before and after amphetamine administration are compared, the reduction of ^{11}C-raclopride receptor binding indicates the amount of dopamine that was released.

Box 2: the OCD family study

- A group of 45 OCD patients were enrolled through NOCDA, online advertisements and outpatient clinics.
- Each participating patient was asked if a sibling could be contacted and a sibling was enrolled when he or she did not meet criteria for OCD and did not use psychotropic medication. About half of the patients had a sibling that participated in the study (19 siblings)
- A control group was matched to the OCD patients on gender, age, education level and handedness and a total of 39 participants were enrolled.
- MRI data of some participants were excluded after scanning because of pathological lesions on the structural scan, a failure in task performance during scanning, technical problems with a specific task or movement. Exclusion of one scan did not necessarily mean that the subject had to be excluded from the other studies. Hence, each study has a slightly different number of subjects included in the analysis.
- During the first visit, all participants filled out an extensive questionnaire, underwent a clinical interview and were familiarized with the different tasks that were to be performed in the scanner. Participants also conducted two extra neuropsychological tasks outside of the scanner (a set shifting task and a planning task). This session took about 1,5 hour.
- Blood samples or mucosal swaps were collected for future genotyping.
- During a second visit, the MRI scans were performed. Subjects were in the MR scanner for about an hour. First a 6 minute resting state fMRI scan was acquired, second a 5 minute structural T1 scan was done, third subjects performed a task that combined OC symptom provocation (by showing pictures that could induce obsessions and compulsions) with cognitive regulation of negative affect. This task took about 25 minutes. Then the n-back working memory task and the stop-signal (response inhibition) task were performed, each lasting for about 15 minutes. Finally, a diffusion tensor imaging (DTI) scan was acquired, to investigate white matter integrity.
- OCD patients and controls, but not siblings had a second MRI session to test the effect of non-invasive brain stimulation (with repetitive Transcranial Magnetic Stimulation; rTMS) on their performance during the symptom provocation and emotion regulation task.
- The results of DTI, the emotion regulation task, and the effect of rTMS are described in different papers that are not part of this thesis.